



**UNIVERSITÉ  
DE GENÈVE**

**FACULTÉ DE MÉDECINE**

**DEPARTMENT OF GENETIC MEDICINE & DEVELOPMENT**

**CMU - Rue Michel Servet 1 / CH-1211 Genève 4**  
phone. +41(0)22 379 54 83- Fax +41(0)22 379 57 06  
[www.unige.ch/medecine](http://www.unige.ch/medecine)

**Professor Emmanouil (Manolis) Dermitzakis**  
[emmanouil.dermitzakis@unige.ch](mailto:emmanouil.dermitzakis@unige.ch)

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Dear Magdalena,

Please find enclosed a manuscript entitled: "Transcriptome and genome sequencing uncovers functional variation in human populations" by Lappalainen and colleagues that we submit to Nature for consideration for publication as an article.

In this paper we characterize regulatory variation in the human genome with higher precision than ever before by integrating high-quality transcriptome sequencing data from hundreds of individuals and genome sequencing data from the 1000 Genomes project. Specifically, we think the paper is appropriate for Nature for the following reasons:

- 1) We characterize transcriptome variation within and between human populations, describing for the first time e.g. how splicing variation contributes disproportionately to continental differences, and how miRNA expression levels correlate to mRNA levels genome-wide.
- 2) Identifying over 8000 genetic loci that affect various transcriptome traits gives us the opportunity to further dissect these variants and their functional mechanisms. For example, we show that variation in gene expression and transcript structure is largely due to independent genetic variants in distinct regulatory elements.
- 3) Genome sequencing data allows us to predict causal regulatory variants, and we apply this to pinpoint likely causal variants of dozens of GWAS associations. Furthermore, we quantify transcriptome effects of hundreds of loss-of-function variants. These results demonstrate the direct utility of transcriptome and genome sequencing data in understanding causal variants underlying human variation in disease and other phenotypes.
- 4) We provide an important openly accessible resource data set for the human genomics community. Furthermore, with our high-quality RNA-sequencing data and analytical contributions from leading laboratories in all steps of the analysis, we anticipate that our study will serve as a model of analysis of genetic effects on transcriptome variation.

The length of the manuscript is 3400 words, and it includes 4 Figures, 1 Table, 34 Supplementary Figures, and 6 Supplementary Tables.

We hope you will find the paper interesting. Looking forward to hearing from you soon.

Sincerely,

Emmanouil Dermitzakis

Tuuli Lappalainen